

- R<sub>1</sub> represents hydrogen or a (C<sub>1</sub>-C<sub>4</sub>)alkyl;
- R<sub>2</sub> represents:
- . a (C<sub>3</sub>-C<sub>7</sub>)alkyl group,
  - . an indan-1-yl or 1,2,3,4-tetrahydronaphthalen-1-yl group, said groups being unsubstituted or substituted by a halogen atom and/or a methyl group;
  - . a saturated, single-nitrogen heterocyclic radical of 5 to 7 atoms, the nitrogen atom being substituted by a (C<sub>1</sub>-C<sub>4</sub>)alkyl, benzyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxycarbonyl or (C<sub>1</sub>-

C<sub>4</sub>)alkanoyl group;

. a group NR<sub>9</sub>R<sub>10</sub>;

. a group (CH<sub>2</sub>)<sub>n</sub>R<sub>11</sub>, CH(CH<sub>3</sub>)R<sub>11</sub>,

(CH<sub>2</sub>)<sub>m</sub>N(CH<sub>3</sub>)R<sub>11</sub>;

5 . a C<sub>3</sub>-C<sub>12</sub> nonaromatic carbocyclic radical, unsubstituted or substituted one or more times by a methyl group;

- or R<sub>1</sub> and R<sub>2</sub> together with the nitrogen atom to  
10 which they are attached form either a piperazin-1-yl radical substituted in position 4 by a phenyl or benzyl group, or a piperidin-1-yl radical disubstituted in position 4 by a phenyl or benzyl group and by a (C<sub>1</sub>-C<sub>4</sub>)alkyl or (C<sub>1</sub>-C<sub>3</sub>)alkanoyl  
15 group; the phenyl or benzyl group substituents on the piperazin-1-yl radical or the piperidin-1-yl radical being unsubstituted or substituted by a halogen atom and/or a methyl group;

- R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represent each  
20 independently of one another a hydrogen or halogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or trifluoromethyl group;

- R<sub>9</sub> and R<sub>10</sub> together with the nitrogen atom to which  
25 they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms containing or not containing a second heteroatom selected from O and N, said radical being unsubstituted or

substituted one or more times by a (C<sub>1</sub>-C<sub>4</sub>)alkyl,  
hydroxyl or (C<sub>1</sub>-C<sub>4</sub>)alkoxy group;

- R<sub>11</sub> represents: . a phenyl which is unsubstituted  
or substituted by one or more  
5 substituents selected from a  
halogen atom and a methyl group;  
. a heteroaryl radical of 6 to 10  
atoms containing one or more  
nitrogen atoms;

10 - n represents 1, 2 or 3;

- m represents 0, 2 or 3;

and their salts, their solvates and their hydrates.

The compounds of formula (I) may exist in the  
form of bases or of addition salts with acids. These  
15 salts are advantageously prepared with pharmaceutically  
acceptable acids, although the salts of other acids  
useful, for example, for purifying or isolating  
compounds of formula (I) also form part of the  
invention.

20 An alkyl group is a linear or branched  
radical such as, in particular: methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, *tert*-butyl, n-pentyl,  
isopentyl, n-hexyl or isohexyl, the methyl group being  
preferred for a (C<sub>1</sub>-C<sub>4</sub>)alkyl and the *tert*-butyl,  
25 2-methylbut-2-yl and 3,3-dimethylbut-2-yl groups being  
preferred for a (C<sub>1</sub>-C<sub>6</sub>)alkyl.

A (C<sub>1</sub>-C<sub>6</sub>)alkoxy group is a linear or branched

radical containing 1 to 6 carbon atoms, the methoxy group being preferred.

A halogen atom is a fluorine, chlorine, bromine or iodine atom, fluorine, chlorine or bromine  
5 atoms being preferred.

The C<sub>3</sub>-C<sub>12</sub> nonaromatic carbocyclic radicals comprise monocyclic or polycyclic, fused or bridged radicals. The monocyclic radicals include cycloalkyls, for example, cyclopropyl, cyclobutyl, cyclopentyl,  
10 cyclohexyl, cycloheptyl or cyclooctyl, cyclohexyl and cyclopentyl being preferred. The fused dicyclic or tricyclic radicals, bridged or in spiran form, include for example the radicals norbornyl, bornyl, isobornyl, noradamantyl, adamantyl, spiro[5.5]undecanyl and  
15 bicyclo[2.2.1]heptanyl, with spiro[5.5]undecanyl and bicyclo[2.2.1]heptanyl being preferred.

A saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom such as O or N, embraces radicals  
20 such as morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl, 3,6-dihydropyridin-1-yl and octahydrocyclopenta[c]pyrrol-2-yl, preference being given to the radicals pyrrolidin-1-yl, piperidin-1-yl and morpholin-4-yl.

25 Among the compounds according to the invention preference is given to the compounds of formula (I) in which:

- R<sub>1</sub> represents a hydrogen atom or a (C<sub>1</sub>-C<sub>4</sub>)alkyl group;
- R<sub>2</sub> represents a group NR<sub>9</sub>R<sub>10</sub> or a nonaromatic C<sub>3</sub>-C<sub>12</sub> carbocyclic radical which is unsubstituted or  
5 substituted one or more times by a methyl group;
- R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> represent each independently of one another a hydrogen or halogen atom or a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or trifluoromethyl group;
- 10 - R<sub>9</sub> and R<sub>10</sub> together with the nitrogen atom to which they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom selected from O and N, said radical being unsubstituted or  
15 substituted one or more times by a (C<sub>1</sub>-C<sub>6</sub>)alkyl group;

and their salts, their solvates and their hydrates.

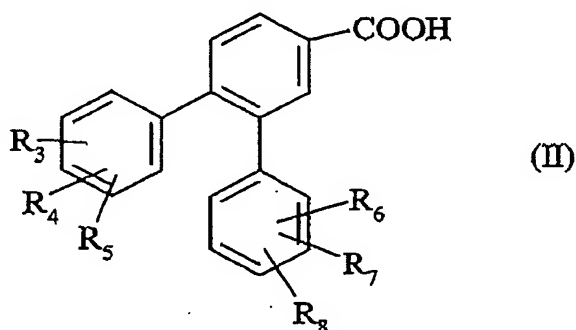
Among the compounds provided by the invention mention may be made of the preferred compounds which  
20 are defined by the following values for the substituents:

- R<sub>1</sub> represents a hydrogen atom; and/or
- R<sub>2</sub> represents a group selected from piperidin-1-yl, pyrrolidin-1-yl, cyclohexyl, spiro[5.5]undecanyl  
25 and 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl;  
and/or
- at least one of the substituents R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>

represents a halogen atom or a trifluoromethyl group; and/or

- at least one of the substituents  $R_6$ ,  $R_7$  and  $R_8$  represents a halogen atom.

5           The present invention further provides a process for preparing compounds of formula (I). This process is characterized in that a functional derivative of terphenylic acid of formula:



10   in which  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are as defined for (I) is treated with an amine of formula  $\text{HNR}_1\text{R}_2$  (III) in which  $R_1$  and  $R_2$  are as defined for (I). Optionally the compound thus obtained is converted into one of its salts and/or solvates.

15           As a functional derivative of the acid (II) it is possible to use the acid chloride, the anhydride, a mixed anhydride, a  $\text{C}_1\text{-C}_4$  alkyl ester in which the alkyl is linear or branched, an activated ester, for example, the *p*-nitrophenyl ester or the appropriately  
20   activated free acid, activated for example with  $\text{N,N}$ -dicyclohexylcarbodiimide or with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

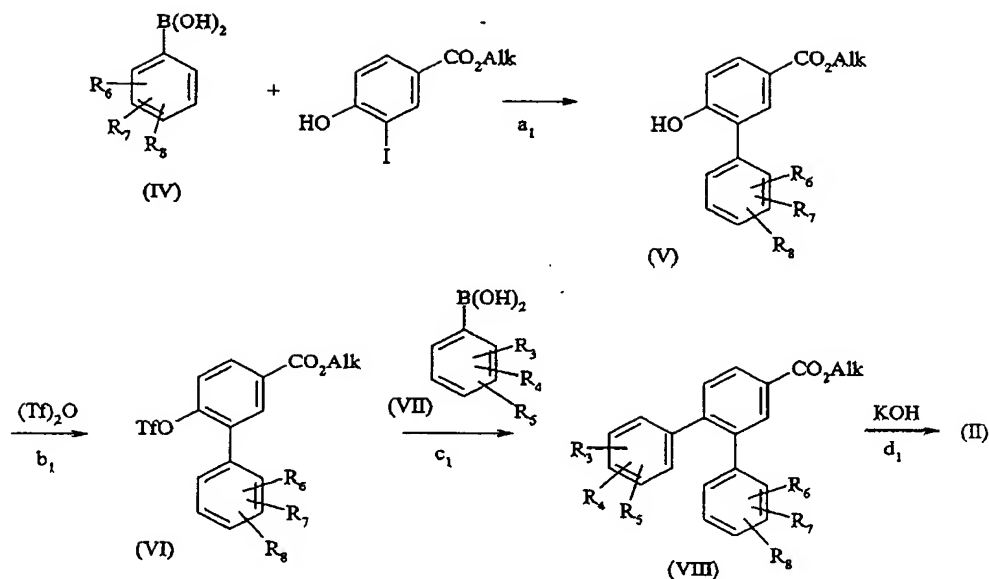
(BOP).

Thus in the process according to the invention the chloride of pyrazol-3-carboxylic acid, obtained by reacting thionyl chloride with the acid of formula (II), can be reacted with an amine  $\text{HNR}_1\text{R}_2$  in an inert solvent such as a chlorinated solvent (dichloromethane, dichloroethane, or chloroform, for example), an ether (tetrahydrofuran or dioxane, for example) or an amide (N,N-dimethylformamide, for example) under an inert atmosphere at a temperature of between  $0^\circ\text{C}$  and the ambient temperature in the presence of a tertiary amine such as triethylamine, N-methylmorpholine or pyridine.

One variant consists in preparing the mixed anhydride of the acid of formula (II) by reacting ethyl chloroformate with the acid of formula (II) in the presence of a base such as triethylamine and in reacting said mixed anhydride with an amine  $\text{HNR}_1\text{R}_2$  in a solvent such as dichloromethane under an inert atmosphere at ambient temperature in the presence of a base such as triethylamine.

The acids of formula (II) can be prepared in accordance with the following scheme:

SCHEME 1



Alk = (C<sub>1</sub>-C<sub>4</sub>)alkyl

In step a<sub>1</sub> the reaction of the organoborate of formula (IV) with an ester of 4-hydroxy-3-iodobenzoic acid is carried out by the method of Farmaco Ed. Sci., 1958, 13, 121, using the conditions described by Suzuki in Helv. Chem. Acta, 1992, 75, 855.

In step b<sub>1</sub>, the product is reacted with triflic anhydride  $(Tf)_2O$  in pyridine in order to prepare the compound of formula (VI). That compound is coupled in step c<sub>1</sub> with an organoborate of formula (VII) under the conditions described in J. Org. Chem., 1992, 57, 379.

The terphenyl ester thus formed is subsequently hydrolyzed by known methods, in the presence of potassium hydroxide, for example, to give the acid of formula (II).



Compounds of formula (II) in which all of the substituents  $R_3$  to  $R_8$  are hydrogen are described in patent US 4,916,145 and in the publication by T. Sato et al., Bull. Chem. Soc. Jap., 1971, 44(9), 2484-2490;

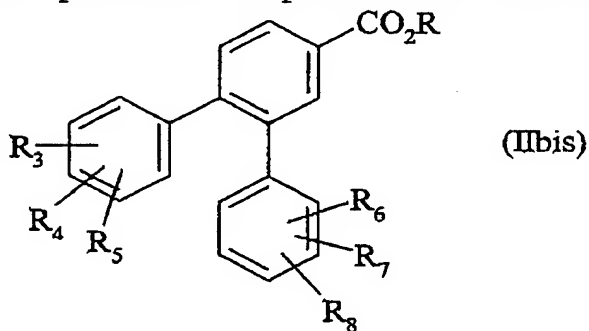
5 the compounds of formula (II) in which the substituents  $R_3$  and  $R_6$  are simultaneously a 3-methoxy, a 4-methoxy or a 3-fluoro, the other substituents  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  being hydrogen, are described in patent US 4,916,145;

the compounds of formula (II) in which the substituents

10  $R_3$ ,  $R_4$  and  $R_6$ ,  $R_7$  are simultaneously 3,4-dimethoxy and the substituents  $R_5$  and  $R_8$  are hydrogen are described in the publication by E. Brenna, J. Chem. Soc. Perkin Trans. I, 1998, 901-904.

The other acids of formula (II) and their

15 esters of formula (VIII) are new and constitute a final aspect of the invention. Accordingly, the present invention also provides compounds of formula:



in which  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are as defined for (I)

20 and  $R$  represents a hydrogen atom or a  $(C_1-C_4)$  alkyl group, on condition that  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are not simultaneously hydrogen, and on condition that,

when R<sub>4</sub>, R<sub>5</sub>, R<sub>7</sub> and R<sub>8</sub> represent hydrogen, R<sub>3</sub> and R<sub>6</sub> do not simultaneously represent a fluorine atom in meta position, or a methoxy group in meta or para position, and on condition that when R<sub>5</sub> and R<sub>8</sub> represent hydrogen  
5 R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub>, R<sub>6</sub> do not simultaneously represent 3,4-dimethoxy groups.

More particularly preference is given to the compounds of formula (IIa) in which:

- R<sub>3</sub> is in position 4 and represents a halogen atom  
10 or a trifluoromethyl group;
- R<sub>6</sub> is in position 2 and represents a hydrogen or halogen atom;
- R<sub>7</sub> is in position 4 and represents a halogen atom;
- R<sub>4</sub>, R<sub>5</sub> and R<sub>8</sub> are hydrogen.

15 The amines HNR<sub>1</sub>R<sub>2</sub> (III) are known or are prepared by known methods; by way of example mention may be made of: Chem. Ber. 1986, 119, 1413-1423.

The compounds of the formula (I) possess very good *in vitro* affinity ( $IC_{50} \leq 10^{-7}$  M) for cannabinoid  
20 receptors CB<sub>1</sub>, under the experimental conditions described by M. Rinaldi-Carmona et al. (FEBS Letters, 1994, 350, 240-244).

The antagonist nature of the compounds of formula (I) is demonstrated by the results obtained in  
25 adenylate cyclase inhibition models as described in M. Rinaldi-Carmona et al., J. Pharmacol. Exp. Ther., 1996, 278, 871-878.

The toxicity of the compounds of formula (I) is compatible with their use as a medicinal product.

In accordance with another of its aspects the present invention provides for the use of a compound of  
5 formula (I), or of one of its pharmaceutically acceptable salts, solvates or hydrates, for preparing medicinal products intended for treating diseases involving CB<sub>1</sub> cannabinoid receptors.

For example and without limitation, the  
10 compounds of formula (I) are useful as psychotropic medicinal products, particularly for treating psychiatric disorders, including anxiety, depression, mood disorders, insomnia, disorders involving delirium, obsessive disorders, psychoses in general,  
15 schizophrenia, and also for treating disorders linked to the use of psychotropic substances, particularly in the case of substance abuse and/or substance addiction, including alcohol addiction and nicotine addiction.

The compounds of formula (I) according to the  
20 invention can be used as medicinal products for treating migraine, stress, diseases of psychosomatic origin, panic attacks, epilepsy, locomotor disorders, especially dyskinesias or Parkinson's disease, shaking and dystonia.

25 The compounds of formula (I) according to the invention can also be used as medicinal products in treating memory disorders, cognitive disorders,

especially in treating senile dementia and Alzheimer's disease, and also in the treatment of attention disorders or vigilance disorders. In addition the compounds of formula (I) may be useful as

5 neuroprotective agents, in treating ischemia and cranial traumas and in treating neurodegenerative diseases, including chorea, Huntingdon's chorea and Tourette's syndrome.

The compounds of formula (I) according to the  
10 invention may be used as medicinal products in treating pain: neuropathic pain, peripheral acute pain, and chronic pain of inflammatory origin.

The compounds of formula (I) according to the invention may be used as medicinal products in treating  
15 appetite disorders, cravings (for sugars, carbohydrates, drugs, alcohols or any appetizing substance) and/or eating disorders, especially as anorexigenic agents or for treating obesity or bulimia, and also for treating type II diabetes or non-insulin-  
20 dependent diabetes. Moreover, the compounds of formula (I) according to the invention may be used as medicinal products in treating gastrointestinal disorders, diarrheic disorders, ulcers, vomiting, urinary and bladder disorders, disorders of endocrine origin,  
25 cardiovascular disorders, hypotension, hemorrhagic shock, septic shock, chronic cirrhosis of the liver, asthma, Raynaud's syndrome, glaucoma, fertility

disorders, inflammatory phenomena, immune system diseases, especially autoimmune and neuroinflammatory diseases such as rheumatoid arthritis, reactional arthritis, diseases resulting in demyelination,  
5 multiple sclerosis, infectious and viral diseases such as encephalitis, cerebrovascular accidents, and as medicinal products for anticancer chemotherapy and for treating Guillian-Barré syndrome.

According to the present invention the  
10 compounds of formula (I) are especially useful for treating psychotic disorders, especially schizophrenia; for treating appetite disorders and obesity; for treating memory and cognitive disorders; for treating alcohol addiction and nicotine addiction, in other  
15 words for alcohol withdrawal and tobacco withdrawal.

According to one of its aspects the present invention relates to the use of a compound of the formula (I), of its pharmaceutically acceptable salts and of their solvates or hydrates for treating the  
20 disorders and diseases indicated above.

The compound according to the invention is generally administered as a dosage unit.

Said dosage units are preferably formulated in pharmaceutical compositions in which the active  
25 principle is mixed with a pharmaceutical excipient.

Thus, according to another of its aspects, the present invention provides pharmaceutical

compositions comprising as active principle a compound of formula (I), one of its pharmaceutically acceptable salts or one of their solvates.

The compound of formula (I) above and the  
5 pharmaceutically acceptable solvates or salts thereof  
can be used at daily doses of from 0.01 to 100 mg per  
kg of body weight of the mammal to be treated,  
preferably at daily doses of from 0.02 to 50 mg/kg. In  
humans the dose can vary preferably from 0.05 to  
10 4000 mg per day, more particularly from 0.1 to 1000 mg  
per day, depending on the age of the individual to be  
treated or on the type of treatment, namely  
prophylactic or curative. Although these doses are  
examples of average situations, there may be particular  
15 cases where higher or lower doses are appropriate, and  
such doses also belong to the invention. In accordance  
with usual practice the dose which is appropriate for  
each patient is determined by the physician according  
to the method of administration and the age, weight and  
20 response of said patient.

In the pharmaceutical compositions of the  
present invention for oral, sublingual, inhaled,  
subcutaneous, intramuscular, intravenous, transdermal,  
local or rectal administration, the active principle  
25 can be administered in unit administration form, as a  
mixture with conventional pharmaceutical vehicles, to  
animals and to humans. The suitable unit administration

forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral solutions or suspensions, sublingual and buccal administration forms, aerosols, topical administration forms,  
5 implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular administration forms and rectal administration forms.

In the pharmaceutical compositions of the present invention the active principle is generally  
10 formulated in dosage units containing from 0.05 to 1000 mg, advantageously from 0.1 to 500 mg, preferably from 1 to 200 mg of said active principle per dosage unit for daily administrations.

In the present description the following  
15 abbreviations are used:

DCM: dichloromethane  
DMF: dimethylformamide  
AcOEt: ethyl acetate  
AT: ambient temperature  
20 m.p.: melting point.

The compounds according to the invention are analyzed by LC/UV/MS coupling (liquid chromatography/UV detection/mass spectrometry). Measurements are made of the molecular peak ( $M^+$ ) and the retention time (t) in  
25 minutes.

An Xterra Waters<sup>®</sup> MS C18 column is used, sold by Waters, measuring  $2.1 \times 30$  mm,  $3.5 \mu\text{m}$ , at ambient

temperature, with a flow rate of 1 mL/minute.

The composition of the eluent is as follows:

- solvent A: 0.025% trifluoroacetic acid (TFA) in water
- 5 - solvent B: 0.025% TFA in acetonitrile.

Gradient: the percentage of solvent B varies from 0 to 100% in 2 minutes with a plateau at 100% of B for 1 minute.

UV detection is carried out between 210 nm  
10 and 400 nm and mass detection in chemical ionization mode at atmospheric pressure.

For interpreting the nuclear magnetic resonance (NMR) spectra the following abbreviations are used: s: singlet; d: doublet; m: unresolved multiplet;  
15 bs: broad singlet; dd: doublet of a doublet.

#### Preparation 1.1

(IIa):  $R_3, R_4, R_5 = 4\text{-Cl}$ ;  $R_6, R_7, R_8 = 2,4\text{-diCl}$ .

Methyl 4-2'',4''-trichloro[1,1';2',1'']terphenyl-4'-carboxylate.

- 20 A) 4-Hydroxy-3-iodobenzoic acid.

30 g of 4-hydroxybenzoic acid are placed in 780 ml of water containing 18 g of sodium hydroxide, 49.5 g of sodium iodide are added, 675 ml of 3.5% sodium hypochlorite solution are run in slowly and the  
25 mixture is left with stirring at AT for 13 hours. 60 ml of concentrated  $\text{H}_2\text{SO}_4$  are added and then, after cooling, the precipitate formed is filtered off and washed with



water. This gives 32.46 g of the expected compound,  
m.p. = 163°C.

B) Methyl 4-hydroxy-3-iodobenzoate.

32.46 g of the acid obtained in the preceding  
5 step is placed in a mixture containing 138 ml of  
methanol and 10.36 ml of concentrated sulfuric acid and  
the mixture is heated at reflux for 3 and a half hours.  
The solvent is concentrated under vacuum and the  
residue is taken up in demineralized water and ethyl  
10 ether. It is neutralized with  $\text{Na}_2\text{CO}_3$  and then the  
aqueous phase is extracted with AcOEt. The extract is  
washed with water and then with a saturated NaCl  
solution. This gives 32 g of the expected compound.

C) Methyl 2',4'-dichloro-6-hydroxy-(1,1'-biphenyl)-  
15 carboxylate.

5.6 g of methyl 4-hydroxy-3-iodobenzoate are  
introduced under argon into 50 ml of anhydrous DMF and  
then 4.2 g of 2,4-dichlorophenylboronic acid and  
5.54 ml of triethylamine and then 240 mg of tri-  
20 orthotolylphosphine are added and the mixture is left  
under argon for 1 hour. 180 mg of palladium acetate are  
added and then the mixture is heated at 100°C for  
4 hours. 2 g of 2,4-dichlorophenylboronic acid, 5.54 ml  
of triethylamine, 120 mg of tri-orthotolylphoshine and  
25 180 mg of palladium acetate are added and then the  
mixture is heated at 100°C for 8 hours. It is  
concentrated under vacuum and the residue is taken up

in AcOEt and then washed with 10% NH<sub>4</sub>OH solution.

Extraction is carried out with AcOEt and the extract is washed with water and then with saturated NaCl

solution. The residue is dried and then chromatographed

5 on silica, eluting with a cyclohexane/AcOEt mixture (82/18; v/v), to give 3.4 g of the expected compound.

D) Methyl 2',4'-dichloro-6-((trifluoromethyl-sulfonyl)oxy)(1,1'-biphenyl)-3-carboxylate.

3.27 g of the compound obtained in the  
10 preceding step are placed in 150 ml of pyridine, the mixture is cooled to between 0°C and 5°C and 2.8 ml of triflic anhydride are run in dropwise. The mixture is maintained with stirring at AT overnight and then concentrated to dryness. The residue is chromatographed  
15 on silica, eluting with a cyclohexane/AcOEt mixture (90/10; v/v), to give 3.2 g of the expected compound.

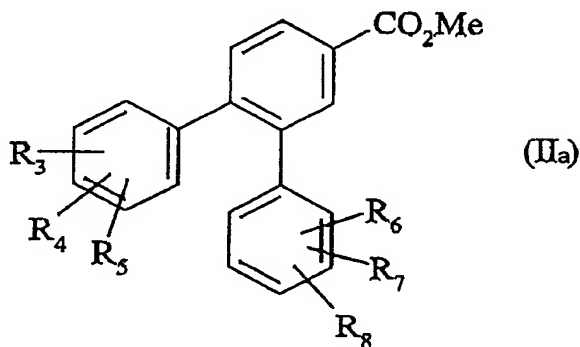
E) Methyl 4,2'',4''-trichloro[1,1';2',1'']terphenyl-4'-carboxylate.

3.2 g of the compound obtained in the  
20 preceding step are placed in 75 ml of toluene and 2.33 g of 4-chlorophenylboronic acid are added and then 1.55 g of potassium carbonate. The mixture is left under argon for 30 minutes and then 1.38 g of tetrakis(triphenylphosphine)palladium are added and the  
25 reaction mixture is heated at between 80°C and 85°C for 3 hours. It is left overnight at AT and then diluted with AcOEt and washed with 5% Na<sub>2</sub>CO<sub>3</sub> solution (twice)

and then with saturated NaCl solution. It is dried and then the residue is chromatographed on silica with a cyclohexane/AcOEt mixture (80/20; v/v) to give 1.83 g of the expected compound, which crystallizes from isopropyl ether, m.p. = 136°C.

The procedure described above is used to prepare the methyl esters of the acids of formula (II) collated in the table below.

TABLE 1

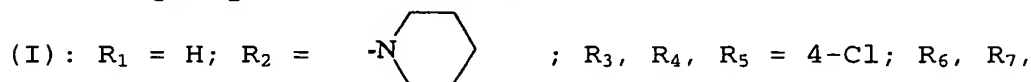


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Preparations	R <sub>3</sub> , R <sub>4</sub> , R <sub>5</sub>	R <sub>6</sub> , R <sub>7</sub> , R <sub>8</sub>	m.p.°C/NMR
1.2	4-Cl	4-Cl	223°C
1.3	4-F	2,4-diCl	NMR (DMSO-d <sub>6</sub> ) δ ppm: 6.9: m: 4H; 7.25: d: 1H; 7.35: dd: 1H; 7.55: m: 2H; 7.80: d: 1H; 8.00: dd: 1H; 13.20: bs: 1H
1.4	4-CF <sub>3</sub>	2,4-diCl	206°C

EXAMPLE 1: Compound I

4,2'',4''-Trichloro(N-1-piperidiny1)[1,1';2',1'']-terphenyl-4'carboxamide.



R<sub>8</sub> = 2,4-diCl

A) 4,2'',4''-Trichloro[1,1';2',1'']terphenyl-4'-  
carboxylic acid.

1.33 g of the compound from Preparation 1.1  
5 is suspended in 30 ml of ethanol, 0.95 g of potassium  
hydroxide in solution in 5 ml of water is added and the  
mixture is heated at reflux for 2 hours. After cooling  
to AT it is filtered over Célite® and concentrated to  
dryness under vacuum. The residue is taken up in 30 ml  
10 of water and then acidified to a pH of 1 by adding 1N  
HCl. The mixture is cooled using an ice bath and then  
extracted with AcOEt. It is washed with water and then  
with saturated NaCl solution to give 1.22 g of the  
expected compound, m.p. = 237°C.

15 B) 4,2'',4''-Trichloro[1,1';2',1'']terphenyl-4'-  
carboxylic chloride.

500 mg of the acid obtained in the preceding  
step are suspended in 50 ml of toluene, 0.3 ml of  
thionyl chloride is added and the mixture is heated at  
20 reflux for 2 hours. The solvent is concentrated twice  
to give 0.52 g of the expected compound in solid form.

C) 4,2'',4''-Trichloro(N-1-piperidinyl)[1,1';2',1'']-  
terphenyl-4'-carboxamide.

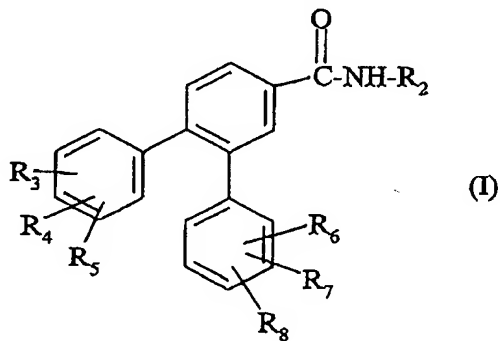
A solution containing 0.17 ml of  
25 aminopiperidine and 0.22 ml of triethylamine in 10 ml  
of DCM is prepared, this solution is cooled to between  
0°C and 5°C and 0.52 g of the acid chloride obtained in

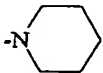
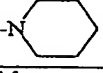
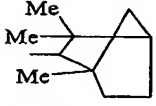
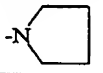
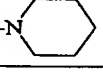

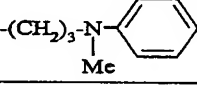
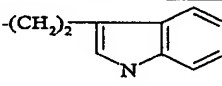
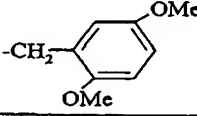


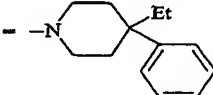
the preceding step in 10 ml of DCM is added dropwise. The mixture is left at +4°C for 2 days. It is poured into ice-water, then extracted with DCM and washed with 5% Na<sub>2</sub>CO<sub>3</sub> solution and then with saturated NaCl

5 solution. The extracts are dried and then the residue is chromatographed on silica, eluting with a toluene/AcOEt mixture (88/12; v/v). This gives 0.3 g of the expected compound, m.p. = 182°C.

The procedure of Example 1 is used to prepare  
10 the compounds of the invention which are described below.

TABLE 2



Compounds	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub> , R <sub>4</sub> , R <sub>5</sub>	R <sub>6</sub> , R <sub>7</sub> , R <sub>8</sub>	Characterization
1	H		4-Cl	2,4-diCl	m.p. = 182°C
2	H		4-Cl	4-Cl	m.p. = 233°C
3	H	 (1S) endo	4-Cl	2,4-diCl	m.p. = 98°C
4	H		4-Cl	2,4-diCl	m.p. = 168°C
5	H		4-F	2,4-diCl	m.p. = 175°C
6	H		4-CF <sub>3</sub>	2,4-diCl	m.p. = 177°C
7	H		4-Cl	4-Cl	M <sup>+</sup> = 489.49 t = 1.95
8	H		4-Cl	4-Cl	M <sup>+</sup> = 484.95 t = 2.33
9	H		4-Cl	4-Cl	M <sup>+</sup> = 492.15 t = 2.28
10	H		4-Cl	4-Cl	M <sup>+</sup> = 411.98 t = 2.43
11	H		4-Cl	4-Cl	M <sup>+</sup> = 450.50 t = 2.43
12	-NR <sub>1</sub> R <sub>2</sub>		4-Cl	4-Cl	M <sup>+</sup> = 514.42 t = 2.50